Cardiac Troponin and Treatment Effects of Omecamtiv Mecarbil: Results From the GALACTIC-HF Study

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G Michael Felker [1], Scott D Solomon [2], Marco Metra [3], John J V Mcmurray [4], Rafael Diaz [5], Brian Claggett [2], David E Lanfear [6], Hans Vandekerckhove [7], Tor Biering-Sørensen [8], Renato D Lopes [9], Alexandra Arias-Mendoza [10], Shin-Ichi Momomura [11], Ramon Corbalan [12], Felix J A Ramires [13], Faiez Zannad [14], Stephen B Heitner [15], Punag H Divanji [15], Stuart Kupfer [15], Fady I Malik [15], John R Teerlink [16]

[1] Division of Cardiology, Duke University and Duke Clinical Research Institute, Durham NC, USA. Electronic address: Michael.felker@duke.edu.
[2] Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
[3] Division of Cardiovascular Medicine Cardiology, ASST Spedali Civili; Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy.
[4] British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK.
[5] Estudios Clínicos Latino América (ECLA), Rosario, Argentina.
[6] Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI, USA.
[7] AZ Sint-Lucas, Ghent, Belgium.
[8] Department of Cardiology, Herlev & Gentofte Hospital and Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[9] Division of Cardiology, Duke University and Duke Clinical Research Institute, Durham NC, USA.
[10] Instituto Nacional de Cardiologìa, Mexico City, Mexico.
[11] Saitama Citizens Medical Center, Saitama, Japan.
[12] Pontificia Universidad Catolica de Chile, Santiago, Chile.
[13] Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.
[14] Université de Lorraine, Inserm, CIC-P 1433, INI CRCT, CHRU Nancy, France.
[15] Cyotkinetics, South San Francisco, CA, USA.
[16] San Francisco Veterans Affairs Medical Center and School of Medicine, University of California-San Francisco, San Francisco, CA, USA.

Abstract

Background:

Omecamtiv mecarbil improves outcomes in patients with heart failure and reduced ejection fraction (HFrEF). We examined the relationship between baseline troponin, change in troponin over time, and the treatment effect of omecamtiv mecarbil in patients enrolled in the Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trial (NCT02929329).

Methods:

GALACTIC-HF was a double-blind, placebo-controlled trial that randomized 8256 patients with symptomatic HFrEF to omecamtiv mecarbil or placebo. High sensitivity troponin I (cTnI) was measured serially at a core laboratory. We analyzed the relationship between both baseline cTnI and change in cTnI concentrations with clinical outcomes and the treatment effect of omecamtiv mecarbil.

Results: Higher baseline cTnI concentrations were associated with a risk of adverse outcomes (hazard ratio for the primary endpoint of time to first HF event or CV death = 1.30; 95% CI 1.28, 1.33, $p < 0.001$ per doubling of baseline cTnI). Although the incidence of safety outcomes was higher in patients with higher baseline cTnI, there was no difference between treatment groups. Treatment with omecamtiv mecarbil led to a modest increase in cTnI that was related to plasma concentrations of omecamtiv mecarbil and peaked at 6 weeks. An increase in

troponin from baseline to week 6 was associated with an increased risk of the primary endpoint ($p < 0.001$) which was similar regardless of treatment assignment (p value for interaction = 0.2).

Conclusions:

In a cohort of patients with HFrEF, baseline cTnI concentrations were strongly associated with adverse clinical outcomes. Although cTnI concentrations were increased in patients treated with omecamtiv mecarbil, we did not find a differential effect of omecamtiv mecarbil on either safety or efficacy based on baseline cTnI status or change in cTnI.

Background:

Omecamtiv mecarbil is a novel activator of cardiac myosin that improves clinical outcomes in patients with heart failure and reduced ejection fraction (HFrEF)[1]. Prior studies have described modest increases in concentrations of circulating cardiac troponin in patients treated with omecamtiv mecarbil, although the mechanism and clinical significance of this finding remains uncertain[2,3]. Elevated concentrations of cardiac troponin are a known risk factor poor outcomes in patients with heart failure and reduced ejection fraction (HFrEF)[4,5]. Troponin elevation in patients with HFrEF may be related to overt myocardial ischemia, although other mechanisms of constitutive troponin release in HFrEF have been proposed and may predominate[6]. The aims of the current analysis were to examine the relationship between baseline troponin, change in troponin over time, and the treatment effect of omecamtiv mecarbil in patients

enrolled in the Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) study.

Methods:

The design, baseline characteristics, and primary results of the GALACTIC-HF study are published [1,7,8]. Briefly, GALACTIC-HF was a global, double-blind, phase 3, placebo controlled randomized clinical trial that compared omecamtiv mecarbil to placebo in 8256 patients with symptomatic HF (NYHA class II-IV) and ejection fraction ≤ 35%. Enrolled patients were required to be currently hospitalized for HF (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for HF within 1 year before screening (outpatients). All the patients had elevated natriuretic peptides (N-terminal pro–B-type natriuretic peptide (NT-proBNP)) level of ≥ 400 pg/mL (1200 pg/mL for patients in atrial fibrillation) or B-type natriuretic peptide (BNP) ≥ 125 pg/mL (375 pg/mL for patients in atrial fibrillation). Optimized background medical therapy was required for enrollment. The study protocol was approved by the relevant local ethics committees and all participants provided informed consent. Twenty-four patients were excluded from the primary analysis due to Good Clinical Practice (GCP) violations, leaving 8232 patients in the analysis dataset.

Troponin Measurement:

Cardiac troponin I (cTnI) was measured serially at a central core laboratory in all patients in GALACTIC-HF using a high sensitivity assay (Siemens ADVIA Centaur Ultra Troponin I, Siemens, Tarrytown, NY), with an 99th percentile upper reference limit of 47 ng/L and a limit of detection

of 1.6 ng/L. cTnI concentrations were measured by protocol at randomization and at 2, 6, 24, and 48 weeks and then every 48 weeks until the end of the study.

Endpoints:

The primary endpoint of GALACTIC-HF was a composite of time to first HF event or death from cardiovascular causes. A heart failure event was defined as an urgent clinic visit, emergency department visit, or hospitalization for subjectively and objectively worsening heart failure leading to treatment intensification beyond a change in oral diuretic therapy. All deaths, HF hospitalizations, urgent HF visits, strokes, myocardial infarctions, hospitalizations for unstable angina, and coronary revascularization procedures were centrally adjudicated by a blinded clinical events committee (Duke Clinical Research Institute, Durham, NC) using published criteria [9].

Statistical Approach

Baseline characteristics for patients classified based on baseline values (above or below the median) were summarized and compared using appropriate summary statistics.

Survival analyses were conducted using Poisson regression models to estimate incidence rates, rate differences, and rate ratios and Cox proportional hazards models to estimate hazard ratios (HRs). For the relationship between baseline cTnI and outcomes, models were adjusted for age, sex, HF etiology, NT-proBNP, diabetes, atrial fibrillation, inpatient vs outpatient randomization, estimated glomerular filtration rate, systolic blood pressure, and ejection fraction. To allow for potentially nonlinear associations between covariates of interest and time-to-event outcomes,

restricted cubic splines were utilized in the Poisson regression models. Treatment effect modification was assessed via the introduction of interaction terms between randomized treatment assignment and the corresponding variable of interest. Multivariable linear regression models using log-transformed troponin at week 6 as the outcome were used to identify significant baseline predictors of 6-week troponin change. The prognostic association of the 6-week troponin change was assessed by including the log-transformed troponin ratio (week 6 / baseline) in time-to-event models that were landmarked at the time of the week 6 visit. All analyses were conducted using STATA version 16 (StataCorp, College Station, Texas). All p values <0.05 were considered statistically significant. No adjustments were made for multiple comparisons.

Results:

Baseline cTnI values were available in 99% of patients (8120 of 8232). The median baseline cTnI concentration was 27 ng/L (IQR 14, 51), and baseline cTnI concentrations were elevated above the 99th percentile upper reference limit (47 ng/L) in 28% (2237 of 8120) of patients with available cTnI data. Baseline characteristics of the study population divided by median baseline cTnI values are shown in **Table 1**. Patients with higher baseline cTnI values were more likely to be randomized as inpatients, and generally had markers of more severe heart failure, including a higher proportion of ischemic heart failure etiology, worse NYHA class, more atrial fibrillation, lower estimated glomerular filtration rate (eGFR), and higher NT-proBNP.

Baseline troponin and Risk of Adverse Outcomes

Higher baseline cTnI concentrations were associated with a higher risk of adverse outcomes. A histogram of baseline cTnI values and the cubic spline curve for the risk of the primary endpoint is shown in **Figure 1**. The hazard ratio for the primary endpoint was 1.30; (95% CI 1.28, 1.33, p < 0.001) per each doubling of baseline cTnI. For placebo-treated patients, the rate of the primary endpoint was approximately twice as high in those with cTnI above the median (39 events per 100 pt-years) compared to those with cTnI below the median (17 events per 100-pt-years). Data were similar for the risk of cardiovascular death (hazard ratio = 1.40; 95% CI 1.36-1.44, p < 0.001) per doubling of baseline cTnI) and myocardial infarction (HR = 1.31; 95% CI 1.22, 1.42, p < 0.001 per doubling of baseline cTnI). The relationship between baseline cTnI persisted after multivariable adjustment for both the primary endpoint (HR = 1.18 (1.15, 1.20), p<0.001) and for cardiovascular death (HR = 1.27 (1.23, 1.31), p<0.001).

Effect of baseline troponin on efficacy and safety of omecamtiv mecarbil

The primary clinical outcomes stratified by baseline cTnI status and treatment assignment are shown in **Table 2**. For the primary endpoint of time to first heart failure event or cardiovascular death, there was a nominally greater treatment effect of omecamtiv in patients with cTnI at or below the median (HR 0.85; 95% CI 0.76, 0.96, ARR = 2.8 per 100 pt-years) compared to patients with cTnI above median (HR 0.96; 95% CI 0.88, 1.05, ARR = 1.5 per 100 pt-years), but this interaction was not statistically significant whether cTnI was split at the median (interaction p value= 0.11) or considered as a continuous variable (interaction p value = 0.26) (**Figure 2**). Similar results were found for other trial endpoints (**Table 2**). Kaplan Meier curves by baseline cTnI status for both the primary endpoint and for cardiovascular death are shown in **Central**

Illustration. Safety outcomes of interest stratified by baseline cTnI status and treatment assignment are shown in **Supplemental Table 1**. Key safety outcomes for omecamtiv mecarbil were generally similar based on the baseline cTnI concentration.

Effect of omecamtiv mecarbil on troponin concentrations

Serial cTnI concentrations over time are shown in **Central Illustration**, stratified by treatment arm. As observed in prior studies, post-randomization cTnI concentrations were modestly increased in the population of patients assigned to omecamtiv mecarbil compared to those assigned to placebo, an effect which was greatest at the 6-week timepoint, which corresponded to the end of dose escalation, and attenuated thereafter. At 6 weeks, there was a significant relationship between plasma concentrations of omecamtiv mecarbil and proportional increase in cTnI over baseline ($p < 0.001$) (See **Supplemental Figure 2**).

Predictors and clinical significance of increase in troponin over time

We performed linear regression modeling to identify predictors of increase in troponin concentration from baseline to 6 weeks. The strongest predictors of a larger proportional increase in cTnI from baseline to 6 weeks were lower baseline cTnI levels, randomization to omecamtiv mecarbil vs placebo, and higher NT-proBNP. A complete list of significant predictors is shown in **Table 3**.

We also evaluated the prognostic importance of relative changes in troponin from baseline to 6 weeks (expressed as % change from baseline) to compare the significance of troponin changes in patients randomized to omecamtiv mecarbil vs those randomized to

placebo (see **Figure 3**). In this analysis, an increase in troponin from baseline to 6 weeks was associated with a higher rate of the primary endpoint ($p < 0.001$), but there was no difference in this relationship in patients randomized to omecamtiv mecarbil or placebo (Interaction term by treatment arm $p = 0.20$).

Discussion

In addition to its role in the diagnosis of acute coronary syndromes, troponin is now an established prognostic biomarker in patients with heart failure and has been shown to be a strong independent predictor of outcomes across multiple heart failure populations[10]. The GALACTIC-HF trial represents among the most extensive evaluations of serial troponin measurements in chronic HF, with a total of 43,053 cTnI measurements assessed over a median of 21.9 months of follow up, all measured in a central core laboratory using a high sensitivity assay. The current analysis reports data on the relationship between cTnI concentrations, clinical outcomes, and treatment with omecamtiv mecarbil.

There are several key findings of our analysis. First, higher baseline cTnI was highly associated with adverse clinical outcomes in the GALACTIC-HF trial. This finding is consistent with other data in both acute[11] and chronic heart failure[4], as well as in persons without known cardiovascular disease[12].

Secondly, the treatment effect of omecamtiv mecarbil was not statistically different based on baseline cTnI values, although estimates of the treatment effect tended to be greater in patients with lower baseline cTnI values. This is somewhat in contrast to other analyses of GALACTIC-HF, where patients with higher risk markers (lower EF, worse NYHA class, and recent

hospitalizations) had a greater treatment effect from omecamtiv mecarbil[13,14]. Although we can only speculate about why higher baseline troponin concentration was not associated with greater treatment effect of omecamtiv mecarbil, we note that similar findings have been published for empagliflozin in the EMPEROR Reduced trial[15]. Studies of other effective heart failure therapies have generally similarly shown consistent benefits across baseline troponin concentrations, including for sacubitril-valsartan[16] and dapagliflozin [17]. In patients with HF and preserved EF (HFpEF) in the PARAGON-HF study, treatment with sacubitril valsartan decreased troponin levels compared to valsartan, and there was a relatively weak signal for a treatment interaction between troponin at baseline and the treatment effect of sacubitril valsartan (p for interaction = 0.07)[18].

Finally, as has been shown previously, omecamtiv mecarbil modestly increased concentrations of cTnI, an effect which was greatest at 6 weeks and attenuated thereafter. An increase in cTnI concentration at 6 weeks was predictive of adverse clinical outcomes, but this relationship was not different between those patients assigned to omecamtiv mecarbil compared to placebo.

The mechanisms underlying elevations of troponin in patients with heart failure are not completely understood. Troponin generally correlates with other measures of heart failure severity including NT-proBNP, and in preclinical studies troponin elevation can be produced experimentally by increasing left ventricular filling pressures even in the absence of changes in coronary blood flow[19], potentially suggesting that troponin elevations may be more related to myocardial wall stress rather than to overt myocardial ischemia[20]. Elevations that occur outside

the context of clinical myocardial ischemia, such as with exercise, have been proposed to be related to alternative mechanisms such as changes in cardiomyocyte permeability or apoptosis[21]. To what degree these mechanisms or others may explain the modest elevations in troponin seen with omecamtiv mecarbil therapy is unknown.

Limitations

The current analysis has important limitations. It is a *post hoc* analysis of cTnI data and is therefore subject to the known limitations of this approach. As a clinical trial, GALACTIC-HF enrolled patients who were generally younger than the broader heart failure population and excluded patients with ejection fraction > 35% or severe renal dysfunction (estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m^2). Notable strengths of the current study include a large, well-treated study population, serial measures of cTnI concentration using a core laboratory, and centralized blinded adjudication of clinical events.

Conclusions

In a large well treated cohort of patients with HFrEF, baseline cTnI concentrations were strongly associated with adverse clinical outcomes. Although cTnI concentrations were increased in patients treated with omecamtiv mecarbil, we did not find a differential effect of omecamtiv mecarbil on either safety or efficacy based on baseline cTnI status or change in cTnI.

Table 1. Baseline Characteristics by Median Baseline Troponin Concentration

	Troponin I ≤ 27 ng/mL	**Troponin I > 27 ng/mL**	
	n=4136	n=3984	
Demographics			
Age - yr	63.5 ± 11.7	65.5 ± 10.8	p<0.001
Sex, Female	1074 (26.0%)	650 (16.3%)	p<0.001
Race			p=0.005
Asian	364 (8.8 %)	344 (8.6 %)	
Black	247 (6.0 %)	301 (7.6 %)	
Other	312 (7.5 %)	248 (6.2 %)	
White	3213 (77.7%)	3091 (77.6%)	
Geographic Region			p=0.16
Asia	344 (8.3 %)	324 (8.1 %)	
Eastern Europe/Russia	1367 (33.1%)	1289 (32.4%)	
Latin America	783 (18.9%)	775 (19.5%)	
US And Canada	720 (17.4%)	633 (15.9%)	
Western Europe/South Africa/Australasia	922 (22.3%)	963 (24.2%)	
Randomization Setting: In-patient	762 (18.4%)	1258 (31.6%)	p<0.001
Clinical Characteristics			
Atrial Fibrillation or Flutter at Screening	995 (24.1%)	1220 (30.6%)	p<0.001
Hypertension Hx	2809 (67.9%)	2895 (72.7%)	p<0.001
Type 2 diabetes mellitus	1526 (36.9%)	1738 (43.6%)	p<0.001
History of stroke	336 (8.1 %)	406 (10.2%)	p=0.001
Ischemic heart failure etiology	2071 (50.1%)	2286 (57.4%)	p<0.001
History of Myocardial Infarction	1631 (39.4%)	1757 (44.1%)	p<0.001
History of Coronary Artery Bypass Surgery	558 (13.5%)	744 (18.7%)	p<0.001
History of Percutaneous Coronary Revascularization	1196 (28.9%)	1213 (30.4%)	p=0.13
LVEF - %	27.2 ± 6.1	26.0 ± 6.4	p<0.001
NYHA Classification			p<0.001
Class II	2451 (59%)	1865 (47%)	
Class III	1595 (39%)	1965 (49%)	
Class IV	90 (2%)	154 (4 %)	
KCCQ Total Symptom Score	72.9 [54.2, 89.6]	64.6 [44.8, 85.4]	p<0.001
Outpatient	77.1 [58.3, 91.7]	71.9 [52.1, 89.6]	p<0.001
Inpatient	57.3 [37.5, 76.0]	51.0 [31.2, 70.8]	p<0.001

SBP — mmHg	116.6 ± 15.1	116.4 ± 15.6	p=0.59
Heart rate — beats/min	72.0 ± 12.0	72.7 ± 12.2	p=0.011
NT-proBNP — pg/mL	1474 [748, 2834]	2729 [1453, 5622]	p<0.001
Cardiac Troponin I — ng/L	14 [10, 20]	52 [37, 88]	--
eGFR — mL/min/1.73m2	63.2 [48.9, 78.4]	54.1 [40.1, 68.8]	p<0.001
Baseline BMI (kg/m2)	28.6 ± 6.3	28.3 ± 6.0	p=0.033
Baseline Weight (kg)	82.6 ± 20.6	82.4 ± 20.5	p=0.59
Heart Failure Therapies			
ACEi, ARB or ARNi	3710 (89.7%)	3356 (84.2%)	p<0.001
ARNi	868 (21.0%)	703 (17.6%)	p<0.001
BB	3979 (96.2%)	3685 (92.5%)	p<0.001
MRA	3250 (78.6%)	3063 (76.9%)	p=0.07
SGLT2 Inhibitors	89 (2.2 %)	125 (3.1 %)	p=0.006
Ivabradine	287 (6.9 %)	242 (6.1 %)	p=0.11
Digitalis glycosides	599 (14.5%)	769 (19.3%)	p<0.001
Cardiac Resynchronization Therapy	468 (11.3%)	669 (16.8%)	p<0.001
Implantable Cardioverter Defibrillator	1199 (29.0%)	1369 (34.4%)	p<0.001

Table 2. Study Outcomes by Baseline Troponin Category and Treatment

Outcome by Troponin	Omecamtiv mecarbil		Placebo			
	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)	HR (95% CI); p-value	ARR (per 100 pt-yrs)
Primary Outcome						
cTnI ≤ 27 ng/L	515/2063 (25%)	14.4	597/2073 (29%)	17.1	0.85 (0.76, 0.96); p=0.007	2.8
cTnI > 27 ng/L	980/2003 (49%)	37.2	981/1981 (50%)	38.7	0.96 (0.88, 1.05); p=0.35	1.5
CV Death						
cTnI ≤ 27 ng/L	225/2063 (11%)	5.6	249/2073 (12%)	6.2	0.92 (0.76, 1.10); p=0.34	0.6
cTnI > 27 ng/L	571/2003 (29%)	17.3	533/1981 (27%)	16.3	1.05 (0.94, 1.19); p=0.38	-1.0
HF Hospitalization						
cTnI ≤ 27 ng/L	392/2063 (19%)	10.9	429/2073 (21%)	12.1	0.90 (0.79, 1.04); p=0.15	1.3
cTnI > 27 ng/L	726/2003 (36%)	27.3	728/1981 (37%)	28.4	0.96 (0.87, 1.06); p=0.43	1.1
First HF event						
cTnI ≤ 27 ng/L	406/2063 (20%)	11.3	462/2073 (22%)	13.2	0.87 (0.76, 0.99); p=0.034	1.9
cTnI > 27 ng/L	746/2003 (37%)	28.3	752/1981 (38%)	29.7	0.95 (0.86, 1.05); p=0.34	1.4
All-cause Death						
cTnI ≤ 27 ng/L	328/2063 (16%)	8.1	357/2073 (17%)	8.9	0.92 (0.80, 1.07); p=0.31	0.8
cTnI > 27 ng/L	723/2003 (36%)	21.9	688/1981 (35%)	21.0	1.04 (0.93, 1.15); p=0.51	-0.9

Table 3. Multivariate predictors of troponin I elevation from baseline to week 6. Predictors with p < 0.01 are included).

Covariates	**Ratio (95% CI)**	**p-value**
(n=7469)		
Baseline Troponin (per doubling)	-17% (-18%, -16%)	<0.001
Randomized Treatment	+42% (+38%, +46%)	<0.001
NT-proBNP (log)	+6% (4%, 8%)	<0.001
Age (per 10 years)	+4% (+3%, +6%)	<0.001
Creatinine	+12% (+8%, +16%)	<0.001
Inpatient Status	+7% (+4%, +12%)	<0.001
ICD	+7% (+3%, +11%)	<0.001
Diabetes Mellitus	+5% (+2%, +9%)	0.001
Region (ref = W Europe)		0.002
Eastern Europe	+6% (+2%, +11%)	
Asia	+9% (+2%, +15%)	
Latin America	+1% (-3%. +6%)	
North America	+1% (-4%, +6%)	
LVEF (per 10%)	-4% (-6%, -1%)	0.003
Sex	-5% (-9%, -2%)	0.004
KCCQ	-2% (-3%, -1%)	0.006
CRT	+7% (+2%, +12%)	0.007
Heart Rate (per 10 bpm)	-2% (-3%, 0%)	0.007

Figure Legends

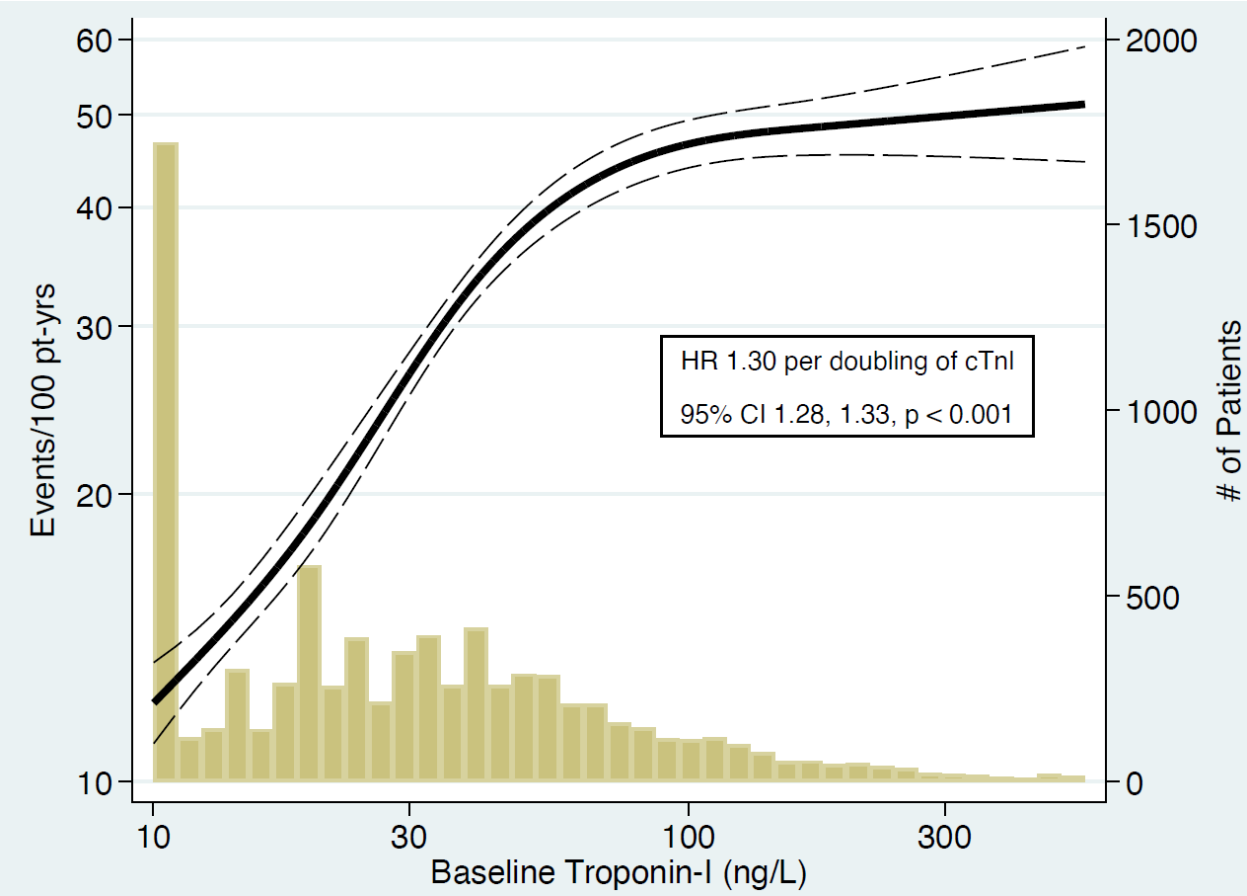
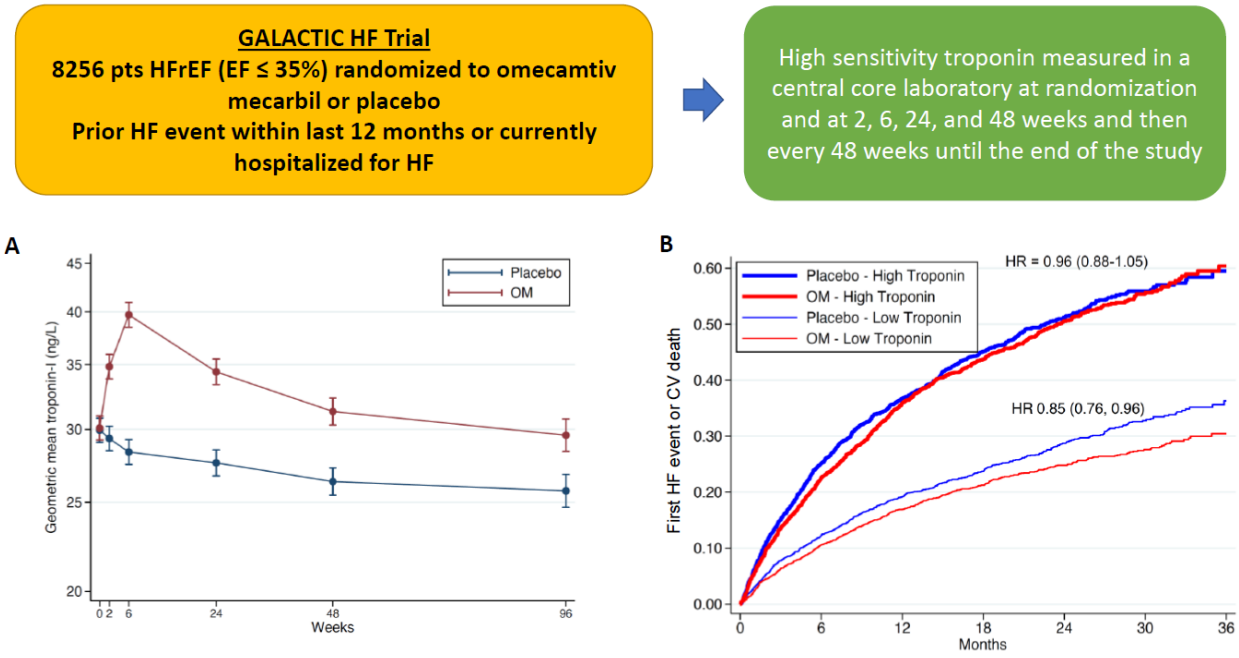
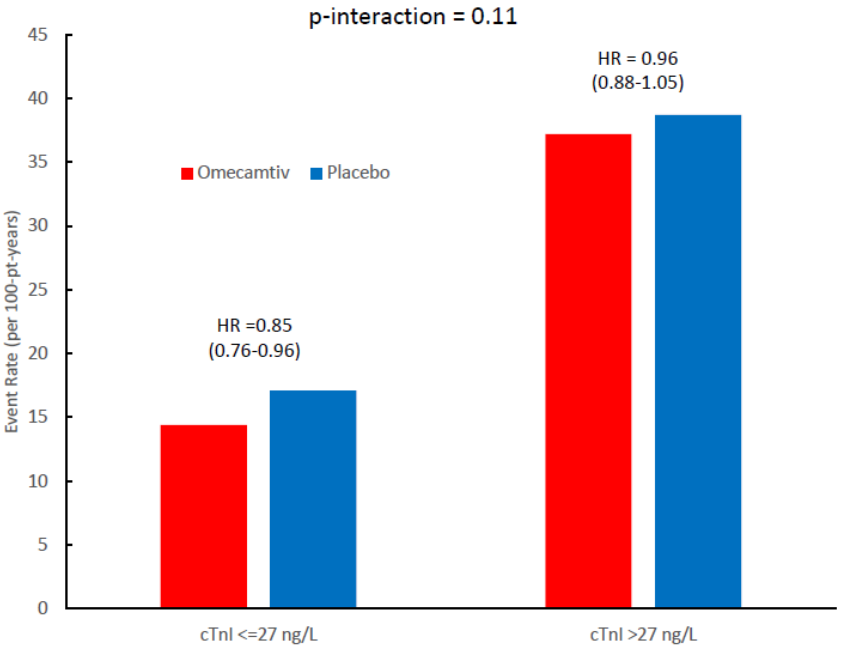


Figure 1. Risk of the Primary Endpoint by Baseline Troponin I Concentration. The distribution of baseline troponin values (histogram) and the cubic spline curve for the hazard of the primary endpoint (time to CV death or first HF event).



Central Illustration. Change in troponin-I concentrations over time for patients randomized to omecamtiv mecarbil or placebo (Panel A). Values shown represent geometric mean, error bars are 95% confidence intervals. Kaplan-Meier curves for the primary endpoint of time to first HF event or CV death, stratified by troponin above or below the median (Panel B).

2A



2 B

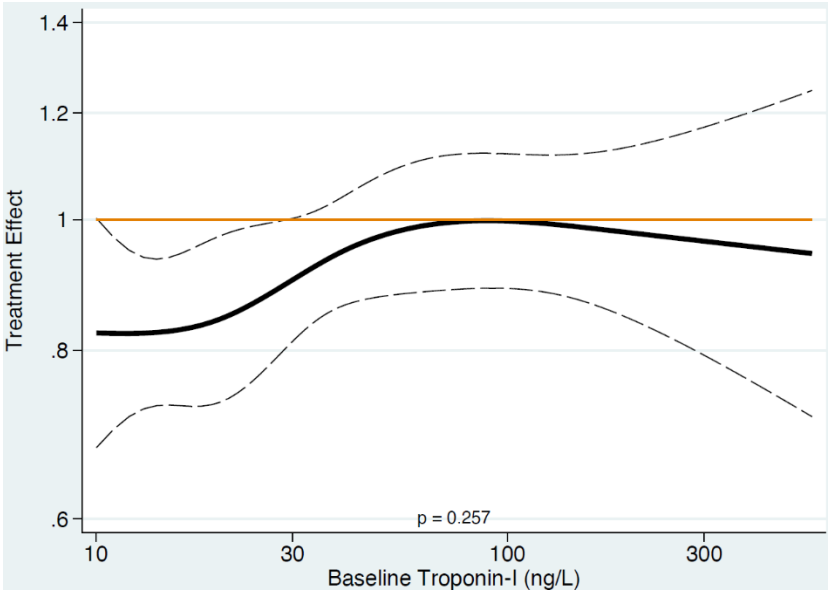


Figure 2. Interaction of baseline troponin I concentration and treatment effect of omecamtiv mecarbil on primary endpoint of time to CV death or first HF event. Treatment effect divided at the median baseline troponin (panel A) and cubic spline function of treatment effect by baseline troponin with 95% confidence intervals (dotted lines) (panel B).

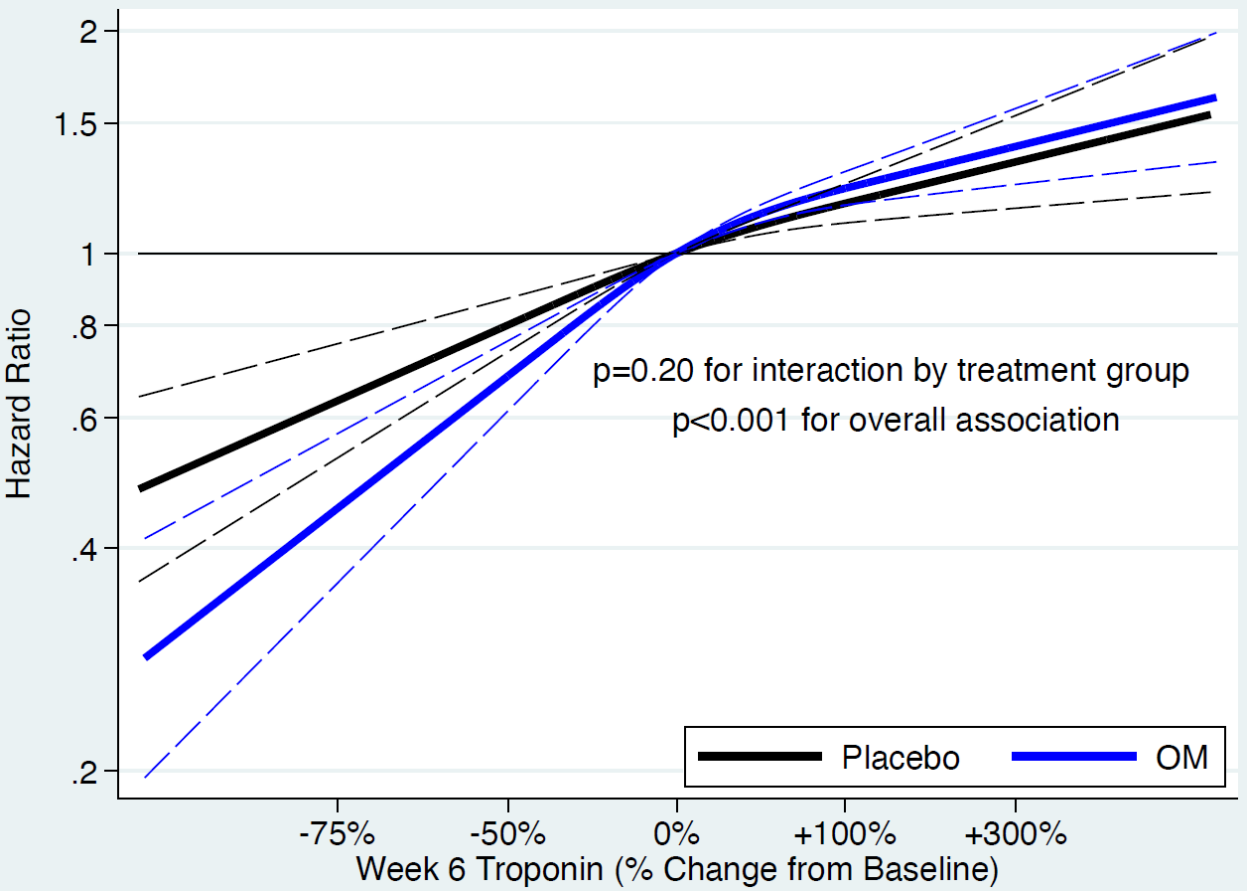


Figure 3. Relationship between change in troponin from baseline to week 6 and the risk of primary outcome by treatment group. Dotted lines represent 95% confidence intervals.

References

1. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sorensen T, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials. *Eur J Heart Fail*. 2020;22:2160–2171.

2. Teerlink JR, Felker GM, McMurray JJV, Solomon SD, Adams KF Jr, Cleland JGF, Ezekowitz JA, Goudev A, Macdonald P, Metra M, et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet*. 2016;388:2895–2903.

3. Teerlink JR, Felker GM, McMurray JJV, Ponikowski P, Metra M, Filippatos GS, Ezekowitz JA, Dickstein K, Cleland JGF, Kim JB, et al. Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure: The ATOMIC-AHF Study. *J. Am. Coll. Cardiol.* 2016;67:1444–1455.

4. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*. 2007;116:1242–1249.

5. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56:1071–1078.

6. Januzzi JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *European Heart Journal*. 2012;33:2265–2271.

7. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Legg JC, Buchele G, Varin C, Kurtz CE, et al. Omecamtiv Mecarbil in Chronic Heart Failure With Reduced Ejection Fraction: Rationale and Design of GALACTIC-HF. *JACC Heart Fail*. 2020;8:329–340.

8. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N. Engl. J. Med.* 2021;384:105–116.

9. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *J. Am. Coll. Cardiol.* 2018;71:1021–1034.

10. Aimo A, Januzzi JL, Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, et al. Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure. *Circulation*. 2018;137:286–297.

11. Felker GM, Mentz RJ, Teerlink JR, Voors AA, Pang PS, Ponikowski P, Greenberg BH, Filippatos G, Davison BA, Cotter G, et al. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17:1262–1270.

12. Jia X, Sun W, Hoogeveen RC, Nambi V, Matsushita K, Folsom AR, Heiss G, Couper DJ, Solomon SD, Boerwinkle E, et al. High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. *Circulation*. 2019;139:2642–2653.

13. Felker GM, Solomon SD, Claggett B, Diaz R, McMurray JJV, Metra M, Anand I, Crespo-Leiro MG, Dahlström U, Goncalvesova E, et al. Assessment of Omecamtiv Mecarbil for the Treatment of Patients With Severe Heart Failure: A Post Hoc Analysis of Data From the GALACTIC-HF Randomized Clinical Trial. *JAMA Cardiol*. 2022;7:26–34.

14. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Biering-Sørensen T, Böhm M, Bonderman D, Fang JC, et al. Effect of Ejection Fraction on Clinical Outcomes in Patients treated with Omecamtiv Mecarbil in GALACTIC-HF. *J. Am. Coll. Cardiol.* 2021;78:97—108.

15. Packer M, Januzzi JL, Ferreira JP, Anker SD, Butler J, Filippatos G, Pocock SJ, Brueckmann M, Jamal W, Cotton D, et al. Concentration-dependent clinical and prognostic importance of high-sensitivity cardiac troponin T in heart failure and a reduced ejection fraction and the influence of empagliflozin: the EMPEROR-Reduced trial. *Eur. J. Heart Fail.* 2021;23:1529–1538.

16. Rørth R, Jhund PS, Kristensen SL, Desai AS, Køber L, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Packer M, et al. The prognostic value of troponin T and N-terminal pro B-type natriuretic peptide, alone and in combination, in heart failure patients with and without diabetes. *European journal of heart failure*. 2019;21:40–49.

17. Berg DD, Docherty KF, Sattar N, Jarolim P, Welsh P, Jhund PS, Anand IS, Chopra V, de Boer RA, Kosiborod MN, et al. Serial Assessment of High-Sensitivity Cardiac Troponin and the Effect of Dapagliflozin in Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial. *Circulation*. 2022;145:158–169.

18. Gori M, Senni M, Claggett B, Liu J, Maggioni AP, Zile M, Prescott MF, Van Veldhuisen DJ, Zannad F, Pieske B, et al. Integrating High-Sensitivity Troponin T and Sacubitril/Valsartan Treatment in HFpEF: The PARAGON-HF Trial. *JACC: Heart Failure*. 2021;9:627–635.

19. Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Troponin Release and Reversible Left Ventricular Dysfunction After Transient Pressure Overload. *J Am Coll Cardiol*. 2018;71:2906–2916.

20. Felker GM, Fudim M. Unraveling the Mystery of Troponin Elevation in Heart Failure. *J. Am. Coll. Cardiol.* 2018;71:2917–2918.

21. Aengevaeren VL, Baggish AL, Chung EH, George K, Kleiven Ø, Mingels AMA, Ørn S, Shave RE, Thompson PD, Eijsvogels TMH. Exercise-Induced Cardiac Troponin Elevations: From Underlying Mechanisms to Clinical Relevance. *Circulation*. 2021;144:1955–1972.